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# Effect of Opioid Versus Non-Opioid Analgesia on Surgical Pleth Index and Biomarkers of Surgical Stress During Neurosurgery for Brain Tumors: Preliminary Findings

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**Abstract:**

**Background:** Stress response to surgery is mediated by the sympathetic nervous system and manifests as changes in hemodynamic and neuroendocrine parameters. Recently, the surgical pleth index (SPI) is employed for objective and continuous monitoring of nociceptive response during surgery. Opioids are the mainstay of managing stress response to nociception during the perioperative period. However, due to the well-known adverse effects of opioids, $\alpha 2$ agonists are increasingly used to ablate stress response and reduce opioid usage.

**Objectives:** This study compared SPI and biomarkers of surgical stress between opioid (fentanyl) and non-opioid (dexmedetomidine) analgesia during craniotomy.

**Methods:** Patients aged 18 to 60 years undergoing elective craniotomies for brain tumor resection under general anesthesia were randomized to receive fentanyl 1 μg/kg/h or dexmedetomidine 0.5 μ/kg/h infusion as the primary intraoperative analgesic. Our objective was to compare SPI and biomarkers of surgical stress—serum cortisol, blood glucose, arterial pH, and leucocyte count between the two groups.

**Results:** Data of all 24 patients recruited into the study were analyzed. There was no difference in the demographic parameters between the groups. The SPI remained similar with both the drugs over various time points during the study period. There was no difference between the groups in the biomarkers of surgical stress—cortisol, blood glucose, and pH while leucocyte count was higher in the fentanyl group.

**Conclusions:** The stress response to surgery during craniotomy for brain tumors is similar with opioid (fentanyl) and non-opioid (dexmedetomidine) analgesia as assessed by SPI and blood markers such as cortisol, glucose, and pH.

**Key Words:**

Biomarkers, neurosurgery, non-opioid analgesia, stress response, surgical pleth index

**Key Message:**

The nociceptive response as assessed by the surgical pleth index and stress response to surgery as assessed by blood biomarkers is similar with opioid (fentanyl) and non-opioid (dexmedetomidine) analgesia during craniotomy for brain tumor resection.

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Noxious stimuli associated with surgery elicit sympathetically mediated stress response that can adversely affect perioperative outcomes.[1] Measuring surgical stress and nociception during the intraoperative period, though important, is not routinely adopted due to a lack of readily available intraoperative stress/nociception monitor. The current surrogates for assessing surgery-induced nociceptive response under anesthesia such as lacrimation, sweating, movement, and increase in heart rate (HR) and blood pressure (BP) are non-specific and unreliable. Recently, an objective parameter, the surgical stress index (SSI) has been used to assess stress response during surgery.[2] The SSI assesses intraoperative stress using photoplethysmographic waveform



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amplitude and heart beat-to-beat interval,[3] and is marketed as surgical pleth index (SPI) in commercially available monitors. The SPI allows quantification of stress response to surgery and hence, effectively any changes to stress response by medications or other interventions.

Apart from hemodynamic activation resulting in tachycardia and hypertension, surgical stress response also manifests as a wide range of endocrinological, immunological, and hematological changes.[4] Among the several neuroendocrine indicators for surgical stress that have been reported, such as pituitary and adrenal hormones, the most commonly studied biomarkers include blood glucose and serum cortisol. Other surrogate markers of surgical stress that can be easily assessed include blood pH and leucocyte count (LC).[5,6]

Opioids are the primary analgesics used to minimize stress response to nociception elicited during the perioperative period. However, due to well-known adverse effects associated with opioids,[7] dexmedetomidine, an alpha-2 agonist, is increasingly used alone,[8-10] or as an opioid-sparing adjuvant during neurosurgeries.[11] Dexmedetomidine, by reducing sympathoadrenal and cardiovascular responses to noxious surgical stimuli, minimizes stress response mediated by the sympathetic nervous system.[4] Additionally, dexmedetomidine reduces opioid consumption and opioid-associated undesirable effects. Also, it is relatively cheaper and easily available, making it accessible in low- and middle-income countries. Despite its potential, dexmedetomidine has not yet replaced opioids for intraoperative analgesia during neurosurgeries. We recently conducted a trial comparing fentanyl and dexmedetomidine in patients undergoing craniotomy for brain tumors and found them comparable for postoperative analgesia.[8] No study has however evaluated the effect of analgesics on stress response and nociception using SPI in the neurosurgical population.[8,12]

The objectives of this study were to compare intraoperative nociception using SPI and surgical stress response using biomarkers between opioid (fentanyl) and non-opioid (dexmedetomidine) analgesia during elective neurosurgery for a brain tumor.

## Methods

This study is a secondary analysis of our published study[8] comparing fentanyl and dexmedetomidine as a primary intraoperative analgesic for perioperative pain relief and opioid consumption during elective craniotomies. The study received a research grant from the Academy of Regional Anaesthesia of India (2017), and the trial was registered with the Clinical Trial Registry of India (CTRI/2017/12/010833). Following ethics committee approval [NIMHANS/IEC (BS & NS DIV) 8th meeting 2017 dated 26-08-2017] and informed consent, patients aged between 18 and 60 years undergoing elective supratentorial brain tumor decompression surgery were screened in March and April 2018. Consented patients were randomized in a 1:1 allocation ratio using a computer-generated random number table by an anesthesiologist not directly involved in the trial, to receive either fentanyl or dexmedetomidine. All patients received standard anesthetic induction with thiopentone 5 mg/kg, fentanyl 1 μg/kg, lignocaine 1.5 mg/kg, and vecuronium 0.1 mg/kg followed by maintenance with oxygen/air/isoflurane titrated to an anesthetic depth of 40-60 on entropy monitor. Bilateral scalp block was performed in all patients after anesthetic induction with 30 mL of 1% lignocaine with 1:200000 epinephrine and 0.25% bupivacaine. The study interventions were administered as fentanyl 1 μg/kg/h or dexmedetomidine 0.5 μg/kg/h, starting from anesthetic induction to skin closure. Hemodynamic activation (>25% increase in HR or mean BP (MBP) from baseline) during surgery despite adequate anesthetic depth was managed with a fentanyl bolus of 50 μg. Apart from standard parameters such as HR, BP, oxygen saturation, end-tidal carbon dioxide, and anesthetic agent levels, SPI was also monitored from a multiparameter patient monitor. Our outcome measures were changes in SPI during surgery and markers of stress response—serum cortisol, random blood glucose (RBG), arterial pH, and LC.

### Surgical pleth index

The SPI (GE Healthcare, Helsinki, Finland) is a score for assessing intraoperative nociception and ranges from 0 to 100, with 100 corresponding to high stress level and 0 corresponding to absent stress. It is computed from normalized heartbeat interval ($HBI_{norm}$) and plethysmographic pulse-wave amplitude ($PPWA_{norm}$) and is derived as follows: SSI = 100–(0.7*$PPWA_{norm}$ + 0.3*$HBI_{norm}$).[3] The SPI appears to be a better measure of nociception/antinociception balance than entropy and HR,[2] and therefore is used to monitor nociceptive stress response to surgery and titrate intraoperative analgesic administration.

#### Biomarkers of stress response

The biomarkers of surgical stress that we evaluated were serum cortisol, RBG, pH, and LC. All samples were collected from an indwelling arterial cannula. The random serum cortisol was measured using electro chemiluminescence immune-assay method from Cobas e-411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The RBG was measured using point of care device, NOCODING One-plus Blood Glucose Meter (ISENS Biosensors India Pvt. Ltd, Gurgaon, India). The pH was obtained from the Eschweiler Combiline blood gas analyzer (Eschweiler GmbH & Co, Kiel, Germany). The LC was estimated in our Clinical Laboratory using an automated hematology analyzer (Beckman Coulter, Miami, USA).

#### Data collection

Baseline demographic characteristics were obtained at the time of consent for all patients. Data regarding SPI were collected every 15 minutes from the beginning to the end of anesthesia. Biomarkers of stress response were collected just before and immediately after the surgery.

#### Statistical analysis

Since this is a preliminary study, no formal sample size was calculated. The collected data were collated offline on the Microsoft Excel worksheet. Continuous variables are represented as means ± standard deviations (SDs) or medians and interquartile ranges (IQRs), depending on normality of distribution of our data as assessed by Shapiro–Wilk test, and categorical variables as frequencies and percentages. We performed repeated-measures analysis of

variance (RMANOVA) for within-group SPI data over various timepoints and mixed model ANOVA for between-group and interaction analysis for SPI. Independent samples *t* test or Mann–Whitney U tests were used as appropriate to compare between the two groups for the post-pre difference in cortisol, RBG, pH, and LC. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 17 (SPSS Inc., Chicago, IL) and $P < 0.05$ was considered statistically significant.

## Results

The data of all patients recruited into the study were analyzed. Figure 1 depicts patient flow into the study. Twenty patients were operated for frontal, temporal or temporoparietal glioma, three for meningioma and one for third ventricle cystic lesion. The mean (SD) age in years in fentanyl and dexmedetomidine group was 42.3 (14.8) and 42.9 (11.3), respectively and mean (SD) weight in kilograms was 62.9 (9.8) and 63.4 (13.8), respectively. The proportion of males in the fentanyl and dexmedetomidine group was six (50%) and eight (66.7%), respectively. Six patients in fentanyl and five patients in dexmedetomidine group received additional fentanyl bolus in the intraoperative period.

### Surgical pleth index

The SPI remained below the threshold of 50 at all timepoints during surgery in both the groups [Figure 2]. There was no significant change in SPI with time in both fentanyl ($F = 0.995$, $\eta^2 = 0.083$, $P = 0.461$) and dexmedetomidine ($F = 0.847$, $\eta^2 = 0.078$, $P = 0.618$) group. Similarly, there was no difference in SPI between fentanyl and dexmedetomidine groups ($F = 0.508$, $\eta^2 = 0.024$, $P = 0.484$ and for group*time interaction $F = 1.170$, $\eta^2 = 0.672$, $P = 0.427$) suggesting that surgical stress response as evaluated by SPI remained similar with both the drugs over various timepoints of study period.

## Biomarkers of Surgical Stress

The changes in biomarkers of surgical stress are shown in Table 1. Serum cortisol level did not change significantly in both groups with analgesic drug infusion. Cortisol level (μg/dL) reported as median and IQR before and after fentanyl infusion was 0.51 (0.39 to 0.67) and 0.51 (0.35 to 4.05), respectively. Similarly, cortisol level before and after dexmedetomidine infusion was 4.28 (0.37 to 14.42) and 2.43 (0.28 to 16.43), respectively. The post-pre difference (median and IQR) in cortisol levels in fentanyl and dexmedetomidine group were -0.09 (-0.19 to 0.37) and -0.03 (-0.21 to 3.19), with $P = 1.000$ and 0.937, respectively for within-group change. There was no significant difference between fentanyl and dexmedetomidine groups for post-pre cortisol differences; $P = 0.630$.

The RBG level increased significantly in both groups during surgery. The RBG level (mg %) reported as mean ± SD before and after fentanyl infusion was 71.67 ± 22.28 and 102.75 ± 24.27, respectively. Similarly, RBG levels before and after dexmedetomidine infusion were 80.33 ± 20.08 and 116.92 ± 25.42, respectively. The post-pre differences (mean ± SD) in RBG levels in the fentanyl and dexmedetomidine group were 31.08 ± 26.91 and 36.58 ± 22.59 with $P = 0.002$ and <0.001, respectively for within-group change. There was no significant difference between fentanyl and dexmedetomidine groups for post-pre RBG difference (MD: 5.5; 95% CI of difference -26.532, 15.532; $P = 0.593$).

The arterial pH decreased non-significantly in both groups during surgery. The arterial pH before and after fentanyl infusion (median and IQR) was 7.41 (7.39 to 7.49) and 7.38 (7.34 to 7.45), respectively. Similarly, pH before and after dexmedetomidine infusion was 7.46 (7.42 to 7.52) and 7.41 (7.40 to 7.47), respectively. The post-pre difference (median and IQR) in pH in fentanyl and dexmedetomidine group was 0.035 (-0.02 to 0.08) and 0.06 (-0.01 to 0.11) with $P = 0.158$ and 0.213, respectively for within-group change. There was no significant difference between fentanyl and dexmedetomidine groups for the post-pre pH difference; $P = 0.551$).

The LC increased in both the groups, with a significant increase in the fentanyl group during surgery. The LC ($10^3/\mu L$) reported as mean ± SD before and after fentanyl infusion was 9.00 ± 3.53 and 16.40 ± 7.39, respectively. Similarly, LC ($10^3/\mu L$) before and after dexmedetomidine infusion was10.67 ± 4.20 and 12.97 ± 5.44, respectively. The post-pre differences (mean ± SD) in LC ($10^3/\mu L$) in fentanyl and dexmedetomidine groups were 7.4 ± 1.46 and 2.3 ± 1.40 with $P < 0.001$ and 0.134, respectively for within-group change. There was significant difference between fentanyl and dexmedetomidine groups for post-pre LC difference (MD 5.09; 95% CI of difference 0.814, 9.366; $P = 0.022$).

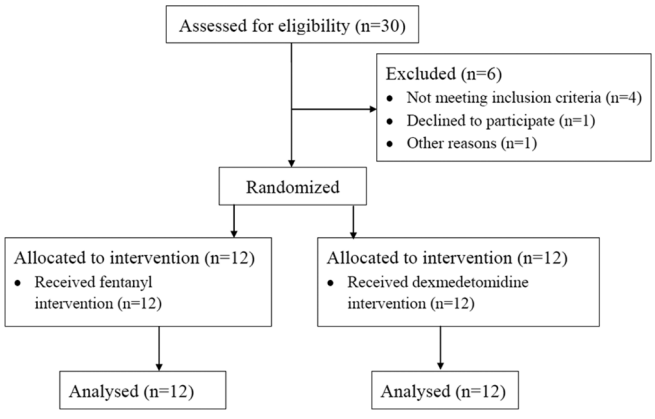


**Figure 1:** Flow diagram depicting patient flow into the study

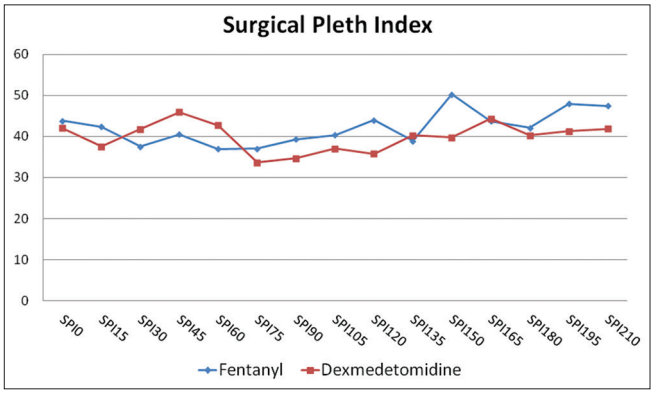


**Figure 2:** Surgical pleth index in the fentanyl and dexmedetomidine group over the infusion timeperiod during surgery

**Table 1: Post-Pre change (after discontinuation and before the beginning of infusion) in the biomarkers of surgical stress with fentanyl and dexmedetomidine analgesia during neurosurgery**

| Measured parameters | Fentanyl (*n*=12) | Dexmedetomidine (*n*=12) | *P* |
|---|---|---|---|
| Serum cortisol (μg/dL) | -0.09 (-0.19 to 0.37) | -0.03 (-0.21 to 3.19) | 0.630 |
| Random blood glucose (mg %) | 31.08±26.91 | 36.58±22.59 | 0.593 |
| Arterial pH | -0.04 (-0.02-0.08) | -0.06 (-0.08 to 0.11) | 0.551 |
| Leucocyte count ($10^3$/μL) | 7.40±1.46 | 2.30±1.40 | 0.022 |

Values are expressed as mean±standard deviation or as median (interquartile range) as applicable; *P*<0.05 is significant

## Discussion

In this study comparing opioid (fentanyl) and non-opioid (dexmedetomidine) drugs for intraoperative analgesia during elective craniotomies, we found no differences in intraoperative stress response to surgery as assessed by SPI and biochemical stress markers of serum cortisol, RBG, and arterial pH. The postoperative LC showed a statistically significant increase in fentanyl group as compared to the dexmedetomidine group, perhaps more as a chance than a true finding.

The SPI has been well-studied as a measure of intraoperative nociception and as a parameter to titrate intraoperative analgesics. In a study comparing SPI-guided versus standard analgesia for laparoscopic cholecystectomy, the authors noted lower SPI values after pneumoperitoneum insufflation but other parameters such as remifentanil consumption, postoperative pain, and recovery from anesthesia were similar.[13] Similarly, Jain *et al.* compared SPI-guided fentanyl analgesia technique with conventional analgesia technique during laparoscopic cholecystectomy. Patients in the SPI group received fentanyl 0.5 μg/kg to maintain SPI between 20 and 50 while patients in the conventional group received fentanyl 0.5 μg/kg when either HR or MBP increased by 20% from baseline. Although intraoperative fentanyl consumption was significantly higher, postoperative visual analog scale score and adjuvant fentanyl requirement were significantly lesser in the SPI group as compared to the conventional group. Drug-related adverse events were similar in both groups.[14] In another study comparing SPI-guided analgesia with conventional analgesia technique in children undergoing adenotonsillectomy, the authors observed reduced fentanyl requirement but similar sevoflurane consumption in the SPI group. However, postoperative emergence agitation and pain were significantly more in the SPI group.[15] In our study, both groups had SPI measurements however, analgesic titration was made based on changes in hemodynamics. We did not find any difference in SPI at any time-point between fentanyl and dexmedetomidine suggesting a similar degree of nociception and analgesia in both the groups. A combination of entropy and SPI results in fewer episodes of hypotension, reduced vasopressor requirement, and fewer doses of fentanyl boluses in critically ill polytrauma patients[16] and should be used when feasible.

Surgical stress results in sympathetic activation and increased adrenal production of cortisol. A recent meta-analysis involving 71 studies with 2953 patients demonstrated that surgical stress response is more pronounced in older patients, women, and in those undergoing open surgery and general anesthesia.[17] However, the anesthetic technique can independently influence stress markers. Total intravenous anesthesia (TIVA) with propofol-remifentanil reduced stress markers of cortisol and glucose as compared to inhalational (isoflurane-remifentanil) technique in patients undergoing laparoscopic surgery.[18]

There are limited data on stress response during neurosurgery with regards to the anesthetic technique. In a study evaluating stress response during craniotomy with two anesthetic techniques, authors observed significantly higher glucose levels with isoflurane-remifentanil when compared to propofol-remifentanil in contrast to similar cortisol levels at various time-points studied.[19] Similar findings were noted in another recent study evaluating stress response to neurosurgery in normotensive and hypertensive patients. Stress markers such as C-reactive protein, blood glucose, and leucocyte levels were reduced with TIVA (propofol-fentanyl infusion) when compared to balanced anesthesia (isoflurane-intermittent fentanyl) technique.[20] We did not observe the difference between fentanyl and dexmedetomidine in the stress markers we studied (cortisol, RBG, and pH) except LC, which was increased in the fentanyl group.

Very few studies have evaluated the effect of intraoperative analgesia on stress response to surgery. Similar changes in hemodynamics and stress hormones—adrenocorticotrophic hormone (ACTH), cortisol, growth hormone, and prolactin were noted in a study comparing two doses of remifentanil infusion, 0.15 and 0.3 μg/kg/min, in 50 patients undergoing laparoscopic cholecystectomy.[21] Similarly, in a study comparing remifentanil with alfentanil TIVA, no difference in plasma concentrations of cortisol, insulin, and glucose was observed in 24 patients undergoing abdominal hysterectomy.[22] We did not observe a difference in stress markers to craniotomy in our study comparing opioid (fentanyl) with non-opioid (dexmedetomidine) analgesia. This finding could be a result of similar surgical stress during craniotomy in both the groups as demonstrated by comparable SPI values. However, a study comparing three analgesic techniques- scalp block, pin-site infiltration and rescue opioid administration for skull-pin insertion, noted significantly reduced levels of stress hormones (ACTH and cortisol) after pin insertion with scalp block.[23]

Our study has important strengths. This is perhaps the first study comparing stress response during neurosurgery using SPI and biomarkers in patients receiving opioid (fentanyl) with non-opioid (dexmedetomidine) analgesia. These outcomes demonstrate that non-opioid analgesia with dexmedetomidine is not inferior to fentanyl, not only in subjective outcomes as observed in our feasibility study,[8] but also in objective measurements of the surgical stress response. This study, however, has several limitations. The small sample size is a major limitation of this trial. Second, we did not compare all

biomarkers of stress response to surgery. Third, given the small number, we did not perform sub-group analysis to evaluate the effect of operative site of craniotomy on the biomarkers of surgical stress. Lastly, the scalp block in both groups may have influenced stress response independent of our study drugs. However, this study encourages further work to generate more robust evidence on this clinically important topic.

## Conclusions

There were no differences in surgical stress response as measured by SPI and serum biomarkers of stress between opioid (fentanyl) and non-opioid (dexmedetomidine) analgesia during brain tumor surgery. Future studies comparing opioid with non-opioid analgesia for stress response to surgery as the primary outcome are required to validate our preliminary findings.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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